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**Declarations under Rule 4.17:**

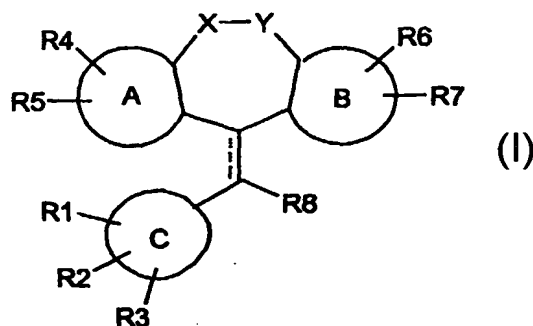
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

[Continued on next page]

(54) Title: TRICYCLIC STEROID HORMONE NUCLEAR RECEPTOR MODULATORS



(57) Abstract: The present invention relates to methods of treating pathological disorders susceptible to steroid hormone nuclear receptor modulation comprising administering to a patient in need thereof an effective amount of a compound of the formula (I): or a pharmaceutically acceptable salt thereof. In addition, the present invention provides novel pharmaceutical compounds of Formula (I), including the pharmaceutically acceptable salts thereof, as well as pharmaceutical compositions which comprise as an active ingredient a compound of Formula (I).



(88) Date of publication of the international search report:  
10 September 2004

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/16213

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/08 C07D221/16 C07D235/14 C07D313/12 C07D401/06  
C07D403/06 A61K31/18 A61K31/553 A61P7/10 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/06137 A (ABBOTT LABORATORIES) 10 February 2000 (2000-02-10) cited in the application  claim 1; table 1	1, 2, 37, 113, 114, 118, 120, 121
X	L.H. WERNER, ET AL.: "Imidazoline derivatives with antiarrhythmic activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 10, no. 4, July 1967 (1967-07), pages 575-582, XP002283810 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US ISSN: 0022-2623 table II, no. 21	37, 40-44, 53-66, 68, 69, 120

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/16213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 351 588 A (M.A. DAVIS, ET AL.) 7 November 1967 (1967-11-07)  the whole document	37,40, 41, 44-46, 53-66, 68,69, 120
X	US 3 519 621 A (L.G. HUMBER) 7 July 1970 (1970-07-07)  example 5	37,38, 40-44, 53-66, 68,69
X	F. GADIANT, ET AL.: "Über neuartige tricyclische Thiazepin- und Thiepin-Derivate" HELVETICA CHIMICA ACTA, vol. 45, no. 6, 20 October 1962 (1962-10-20), pages 1860-1870, XP002283811 VERLAG HELVETICA CHIMICA ACTA, BASEL, CH compounds 11B,13B	37,40, 41,43, 44, 53-66, 68,69, 120
X	GB 1 501 321 A (SUMITOMO CHEMICAL) 15 February 1978 (1978-02-15)  the whole document	37, 40-44, 53-66, 68,69, 120
X	GB 1 001 822 A (SANDOZ) 18 August 1965 (1965-08-18)  example 7	37,40, 41,43, 44, 53-66, 68,69
X	F.J. VILLANI, ET AL.: "Derivatives of 12,11-dihydro-5H-dibenzo[a,d]cycloheptene and related compounds. II" JOURNAL OF MEDICINAL CHEMISTRY, vol. 7, no. 4, July 1964 (1964-07), pages 457-460, XP002283812 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US ISSN: 0022-2623 compounds VIIa-c,VIII; table II	37-45, 53-66, 68,69, 120
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/16213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T. BILLE-SAME, ET AL.: "Fulvènes et éthylènes thermochromes. LXXII. (1) Observations dans la série du dibenzo'a,d!cyclohepta'1,4!diène" BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, no. 11, November 1972 (1972-11), pages 4212-4214, XP002283813 SOCIETE FRANCAISE DE CHIMIE, PARIS, FR ISSN: 0037-8968 compounds 1,4	37-44, 53-66, 68,69
X	A.A. CORDI, ET AL.: "Synthesis and structure-activity of 4(5)-(2,2-diphenylethyl)imidazoles as new alpha2-adrenoreceptor agonists" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 25, no. 7, 1990, pages 557-568, XP002283814 EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR ISSN: 0223-5234 compound 6q; table I	37, 40-42, 44, 53-66, 68,69, 120
X	X.-M. CHENG, ET AL.: "Synthesis and structure-activity relationships of 9-substituted acridines as endothelin-A receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 24, 17 December 1996 (1996-12-17), pages 2999-3002, XP002283815 ELSEVIER SCIENCE PUBLISHERS, OXFORD, GB compound 15	37, 40-42, 44, 53-65, 69,120
X	GB 1 242 096 A (LABAZ) 11 August 1971 (1971-08-11)  page 6, line 20 - line 28; claims 1,5	37, 40-45, 53-66, 68,69, 120
X	J.-M. BASTIAN, ET AL.: "4H-Benzo'4,5!cyclohepta'1,2-b!thiophene" HELVETICA CHIMICA ACTA, vol. 49, 22 January 1966 (1966-01-22), pages 214-234, XP002263672 VERLAG HELVETICA CHIMICA ACTA, BASEL, CH ISSN: 0018-019X compounds 20B,21B,21C	37, 40-42, 44,45, 53-66, 68,69

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/16213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. DAICH, ET AL.: "On the synthesis and reactivity of 4,10-dihydrobenzo[b]thieno- '2,3-e]thiepin-10-acetic acid and 5,10-dihydrobenzo[e]thieno'2,3-b]thiepin- 10-acetic acid" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 29, no. 7, 1992, pages 1789-1795, XP002283816 HETEROCORPORATION, PROVO, US compound 24	37,40, 41,44, 53-66, 68,69
X	H. POLMAN, ET AL.: "Photoaddition of aromatic ketones to some arylacetylenes; formation of alpha,beta-unsaturated ketones and aldehydes" RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS, vol. 92, 1973, pages 845-854, XP008031504 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL ISSN: 0165-0513 table I, products A,G,L,O	37-45, 53-64,69
X	G. WITTIG, ET AL.: "Über Ringerweiterung und Ringverengerung auf der Basis von Ylidisomerisationen" JUSTUS LIEBIGS ANNALEN DER CHEMIE, vol. 594, 1955, pages 89-118, XP008031512 VERLAG CHEMIE, WEINHEIM, DE ISSN: 0075-4617 page 111, line 36 - line 43	37-41, 43,44, 53-65,69
X	GB 1 043 158 A (SANDOZ) 21 September 1966 (1966-09-21)  the whole document	37,40, 41, 43-45, 53-67,69
X	M.A. DAVIS, ET AL.: "New psychotropic agents. VIII. Analogues of amitriptyline containing the normeperidine group" JOURNAL OF MEDICINAL CHEMISTRY, vol. 10, no. 4, July 1967 (1967-07), pages 627-635, XP002284192 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US table I, no. 1	37, 40-42, 44,45, 50, 58-66, 68,69

# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 03/16213

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1-36, 113-119 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 37-69 (in part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 1-36, 113-119 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.2

Claims Nos.: 37-69 (in part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the claims. The search and the report for those claims can only be considered complete for compounds of formula (I) of claim 37 in which rings A, B and C are as defined in claim 39, X-Y is as defined in claim 42, "-----" is as defined in claim 43 and, when C is a phenyl group, R1 is as defined in claims 46-52.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT 03/16213

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0006137	A	10-02-2000	CA 2338968 A1 EP 1100483 A2 JP 2002521430 T WO 0006137 A2	10-02-2000 23-05-2001 16-07-2002 10-02-2000
US 3351588	A	07-11-1967	NONE	
US 3519621	A	07-07-1970	NONE	
GB 1501321	A	15-02-1978	JP 1188764 C JP 51080868 A JP 58017469 B JP 51143679 A AR 213280 A1 AR 212816 A1 AT 346353 B AT 2276 A AU 498463 B2 AU 1002076 A BE 837341 A1 CA 1065310 A1 CH 621781 A5 CH 623816 A5 CS 189735 B2 DE 2600358 A1 DK 2476 A ES 444101 A1 FI 753701 A FR 2296412 A1 NL 7600096 A NO 760018 A ,B, PL 98488 B1 SE 7514779 A US 4085210 A US 4169146 A ZA 7600004 A	30-01-1984 15-07-1976 07-04-1983 10-12-1976 15-01-1979 13-10-1978 10-11-1978 15-03-1978 15-03-1979 14-07-1977 06-07-1976 30-10-1979 27-02-1981 30-06-1981 30-04-1979 08-07-1976 07-07-1976 16-07-1977 07-07-1976 30-07-1976 08-07-1976 07-07-1976 31-05-1978 07-07-1976 18-04-1978 25-09-1979 29-12-1976
GB 1001822	A	18-08-1965	CH 384589 A CY 448 A GB 1001823 A GB 1001825 A MY 5669 A OA 1261 A DE 1199278 B FR 1298662 A GB 1001824 A NL 126586 C NL 267864 A SE 327997 B	30-11-1964 01-08-1968 18-08-1965 18-08-1965 31-12-1969 15-02-1969 26-08-1965 13-07-1962 18-08-1965  07-09-1970
GB 1242096	A	11-08-1971	AT 289103 B BE 742443 A CH 508617 A DE 1963205 A1 DK 125795 B ES 374762 A1 FI 49297 B FR 2026686 A5	13-04-1971 01-06-1970 15-06-1971 09-07-1970 07-05-1973 16-01-1972 31-01-1975 18-09-1970

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1242096	A	IE 33870 B1	27-11-1974
		NL 6917891 A ,B	23-06-1970
		NO 125385 B	04-09-1972
		OA 3193 A	15-12-1970
		SE 367189 B	20-05-1974
		US 3651051 A	21-03-1972
		YU 318369 A ,B	31-12-1977
<hr/>			
GB 1043158	A	21-09-1966 CH 406219 A	31-01-1966
		AT 246140 B	12-04-1966
		AT 249061 B	26-09-1966
		AT 249062 B	26-09-1966
		FR 1359543 A	24-04-1964
		OA 710 A	15-07-1967
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